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Morphological Characterisation of Solid Pharmaceutical Products using X-ray tomography

Frederik Doerr

Bruker microCT User Meeting 2017

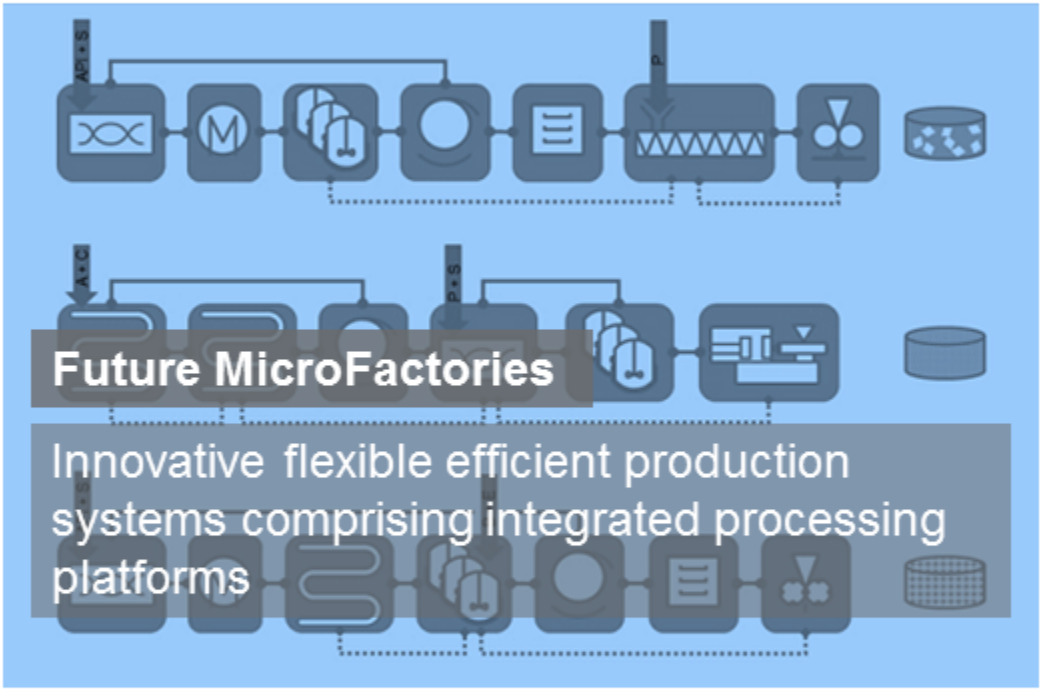
14 June 2017

Overview

- Introduction and Objective
- Hardware: SkyScan 2211
- Image Processing: Extracting relevant Morphological Descriptors
- Case Studies:
    1) Single Particle Analysis
    2) Injection Moulded Tablet (Formulated System)
    3) 3D Printed Tablet (Formulated System)
- Conclusions
- Acknowledgment

CT - Focus and Application

CMAC: Aim for integrated, continuous pharmaceutical MicroFactories supported by a predictive design framework to enable fast product and process development.



Process integration and control require reliable characterisation of a vast variety of pharmaceutical (intermediate) products with complex multi-dimensional solid state attributes.

SkyScan 2211 (nanoCT)

Scanning

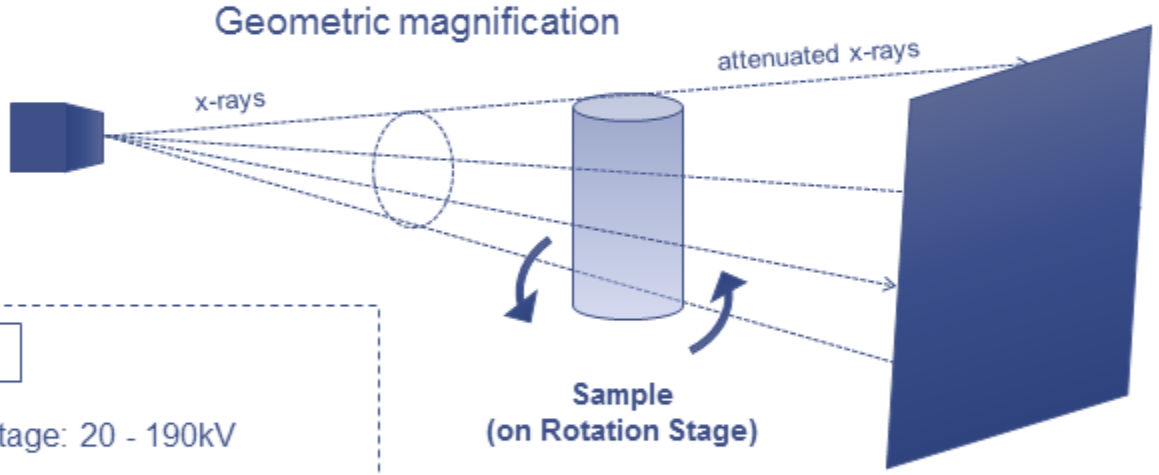
Acquiring raw Data (2D, 14bit images) from sample.

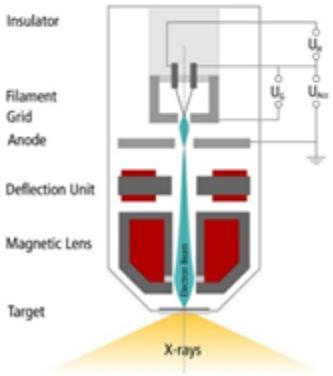
Reconstruction

Transformation of 2D projections into a 3D-reconstruction of the sample

Analysis / 3D Rendering

Image analysis to extract desired sample information. 3D volume rendering to produce an interactive 3D model for visualisation.





X-ray Source

Accelerating voltage: 20 - 190kV

Emission power: 4 W (Be window)

Transmission Target material: Tungsten

Beam spot size: nanomode 900nm, micromode 2um

Detector

- 11Mp CCD-Sensor
- CCD temperature stabilization
- central 4000x2670 pixel, 9um /pixel
- 14bit digitalization, 70dB dynamic range

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Image Processing
Morphological Characterisation

Cross-Section Image (8bit, grayscale)

Histogram-based Thresholding

Binary Image (bw_0)

Noise Reduction

Binary Image (bw_1)

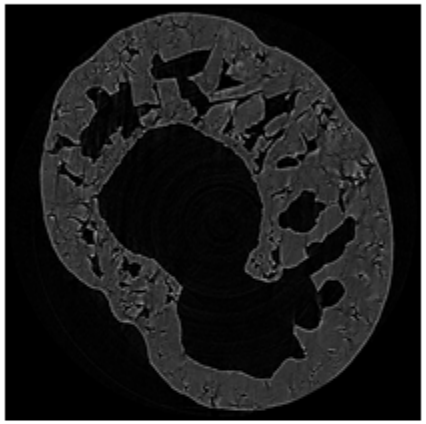
Fill Enclosed Background Areas

Binary Image (bw_2)

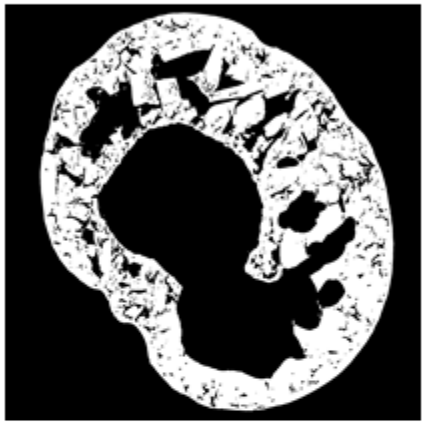
Object Convex Hull

Binary Image (bw_3)

Cross-Section Image



Binary Image (bw_1)



Binary Image (bw_2)

Binary Image (bw_3)

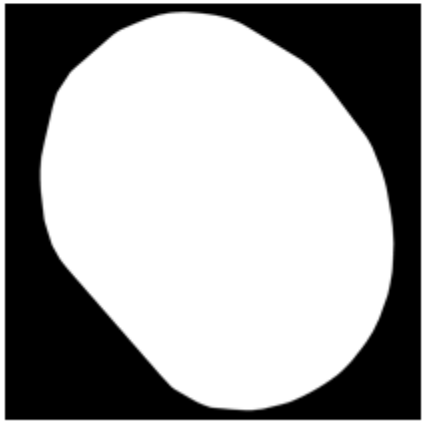


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Image Processing
Image Noise Reduction

Critical step during image processing: Noise Reduction

Binary Image (bw_0)

Noise Reduction

Binary Image (bw_1)

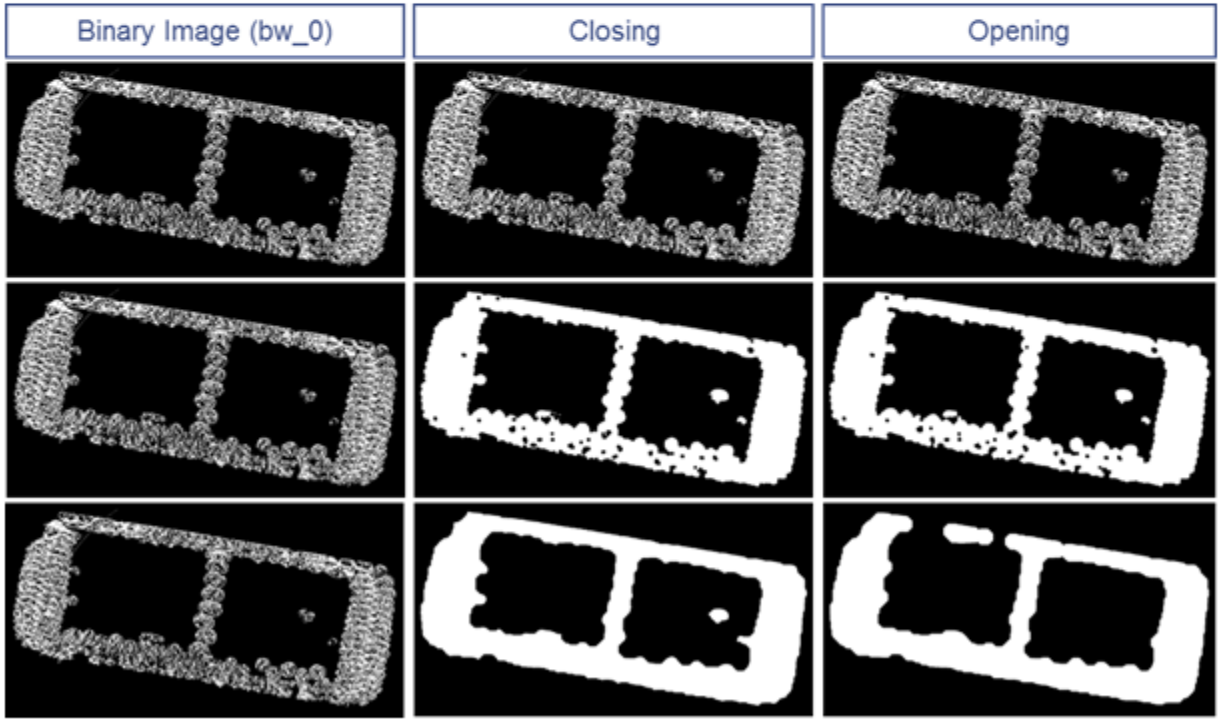
Despeckle and Morphological Operations for Noise Reduction and Elimination of CT-Artefacts

Operation/ Structuring Element

Closing / Opening
Strel: 1 pixel, disk

Closing / Opening
Strel: 10 pixel, disk

Closing / Opening
Strel: 50 pixel, disk



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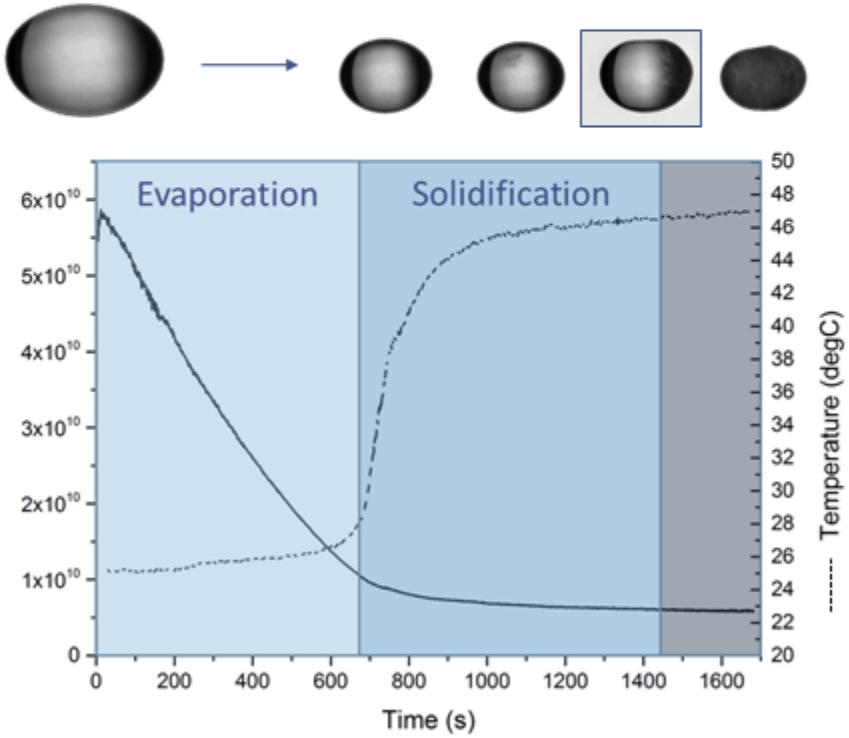
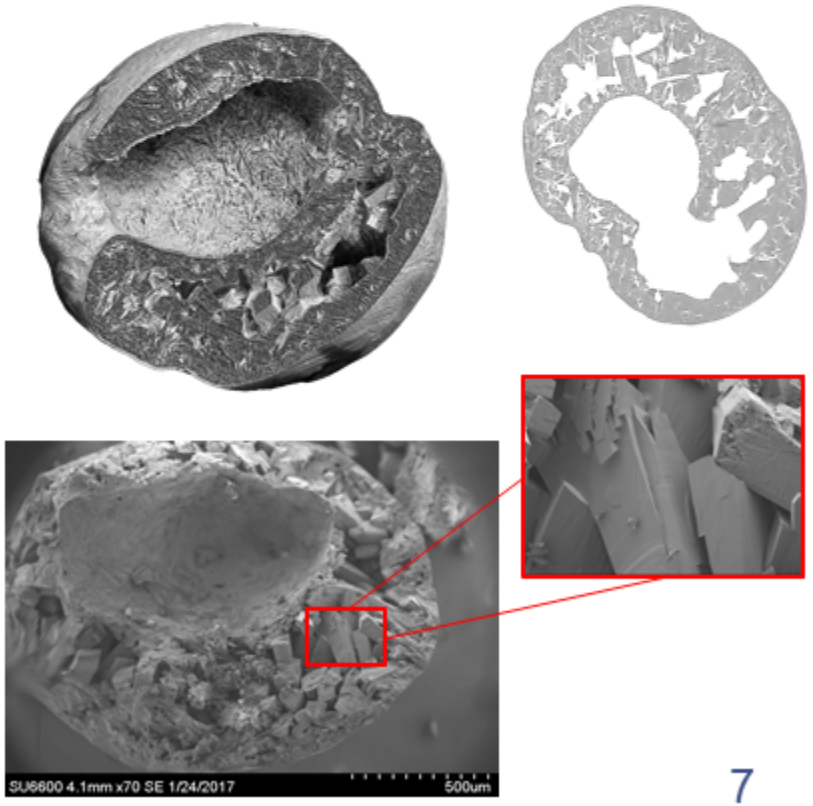
Single Particle Analysis:
Introduction

- Single particle experiments to investigate mechanisms of solid phase formation and drying kinetics
- Lactose - water system, solidification from solution

Single Particle phase formation ➡ CT analysis to examine final particle structure:





Single Particle Analysis:
Visualisation / Structural Characterisation

Analysis Settings:	
Image Pixel Size	2.00 um (CCD-Detector)
Frame Average	8
Source Voltage (kV)=	40 / Current (uA)= 400

Particle Size:	
Major Diameter	1.89 mm
Max Area	2.20 mm^2

Particle Porosity:	
Closed	36.7 %
numClosed	885 +/- 345
Open	3.2 %
numOpen	643 +/- 276
Total	39.9 %

Sphericity	0.69 +/- 0.16

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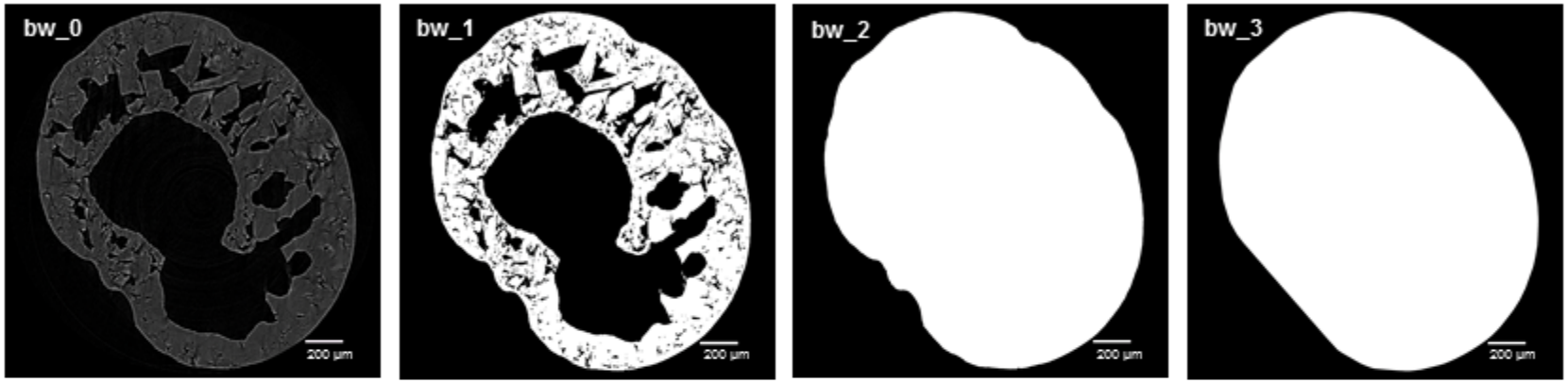
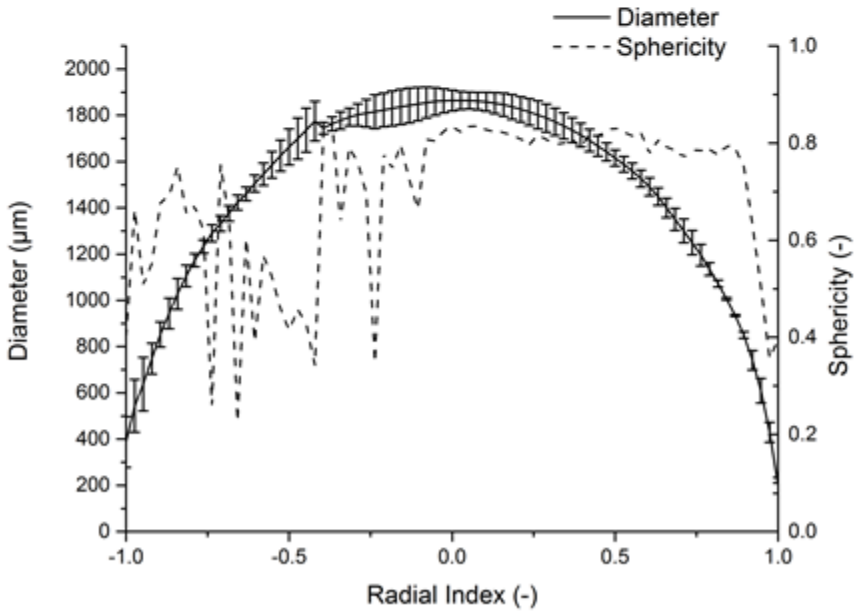
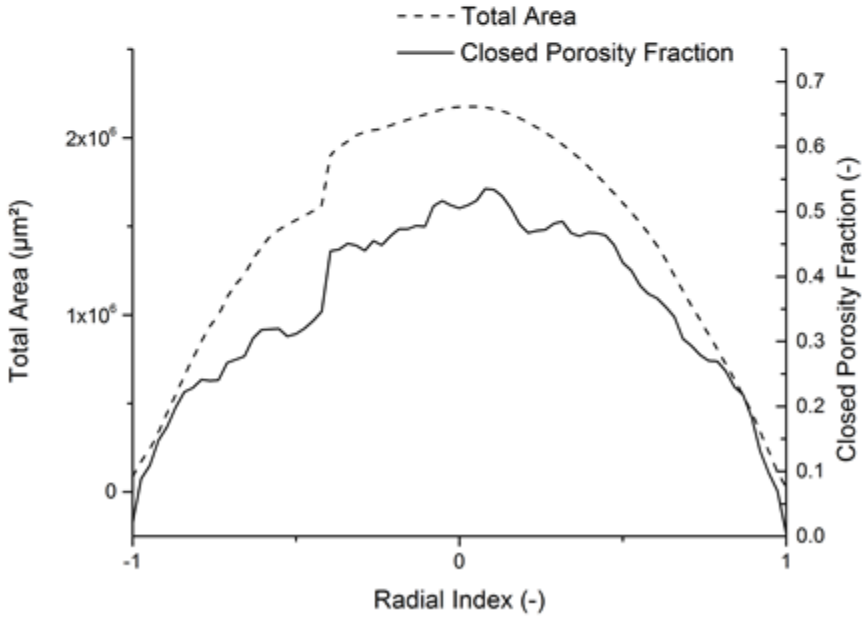
Single Particle Analysis:
Structural Characterisation

2418 recon. cross-section images: Subset 75 cross-sections for structural characterisation



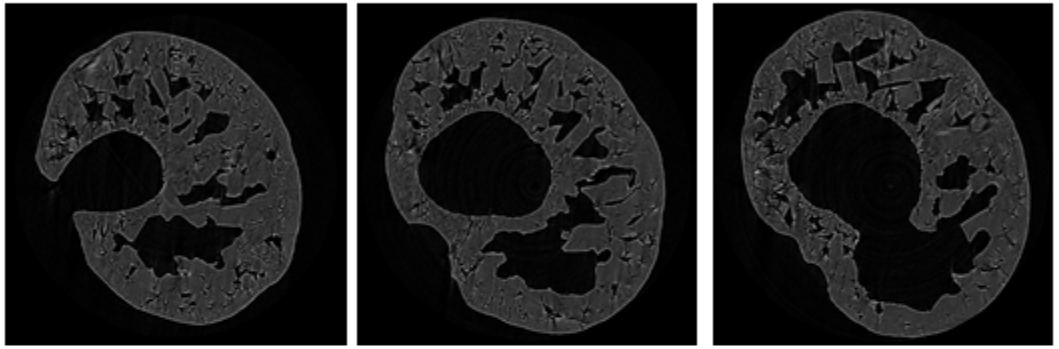


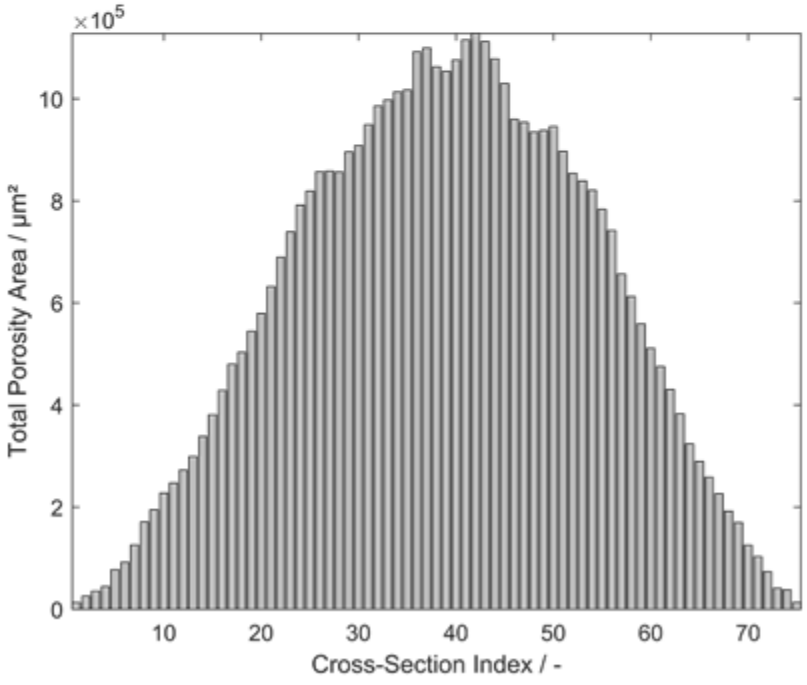


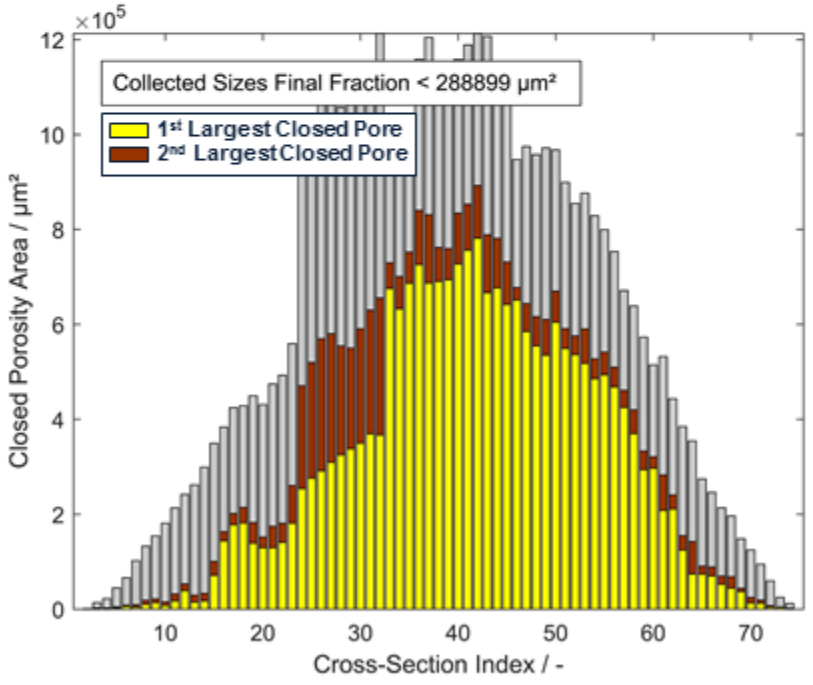
Single Particle Analysis:
Structural Characterisation

2418 recon. cross-section images: Subset 75 cross-sections for structural characterisation

Selected Cross-Sections (Progression of Inner Void):







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Structural Characterisation

2418 recon. cross-section images: Subset 75 cross-sections for structural characterisation

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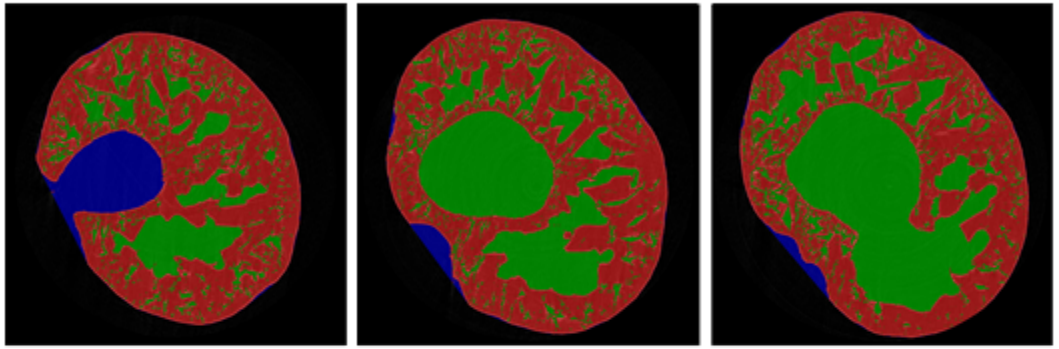
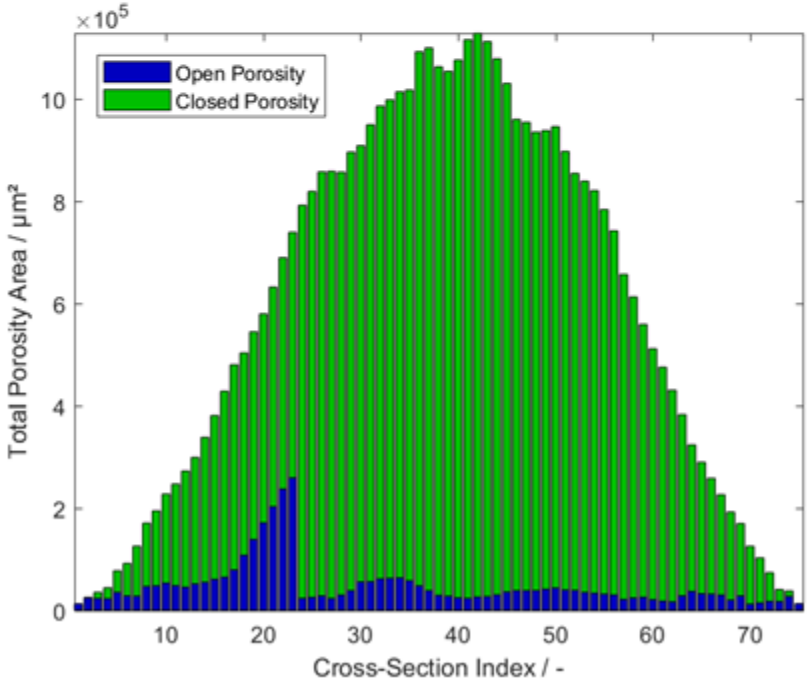
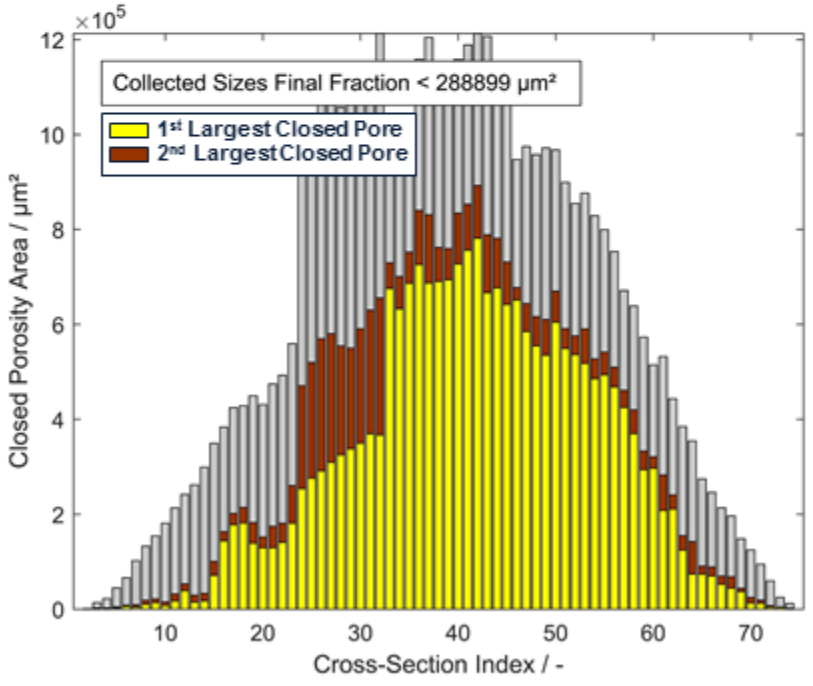




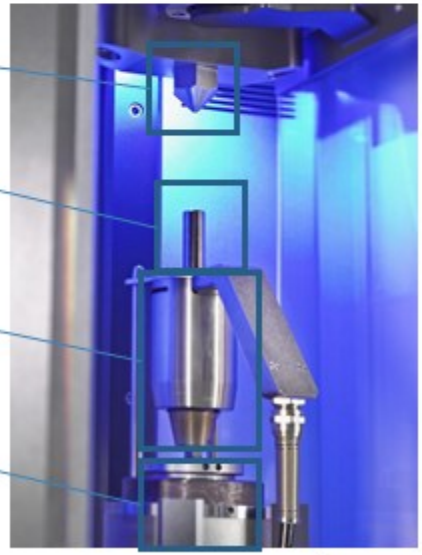


Injection Moulded Tablets:
Introduction

Injection Moulder: Minijet Pro (Thermoscientific HAAKE)

Pre-extruded API – PVP powder blends

Powder Blends → Hot Melt Extrusion → **Injection Moulder**



Pre-extruded

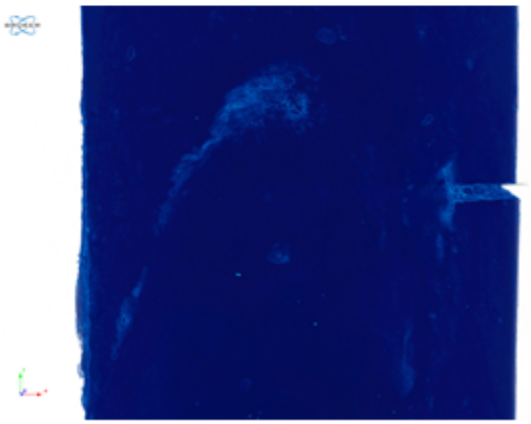
Pre-extruded (not time-stable)

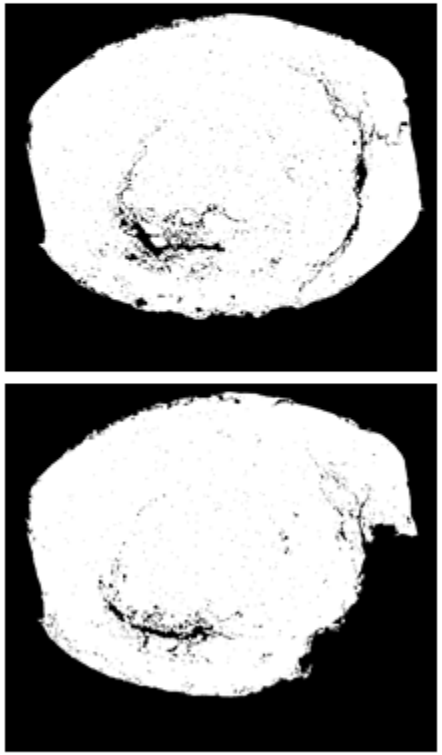
Injection Moulded Tablets:
Visualisation / Structural Characterisation

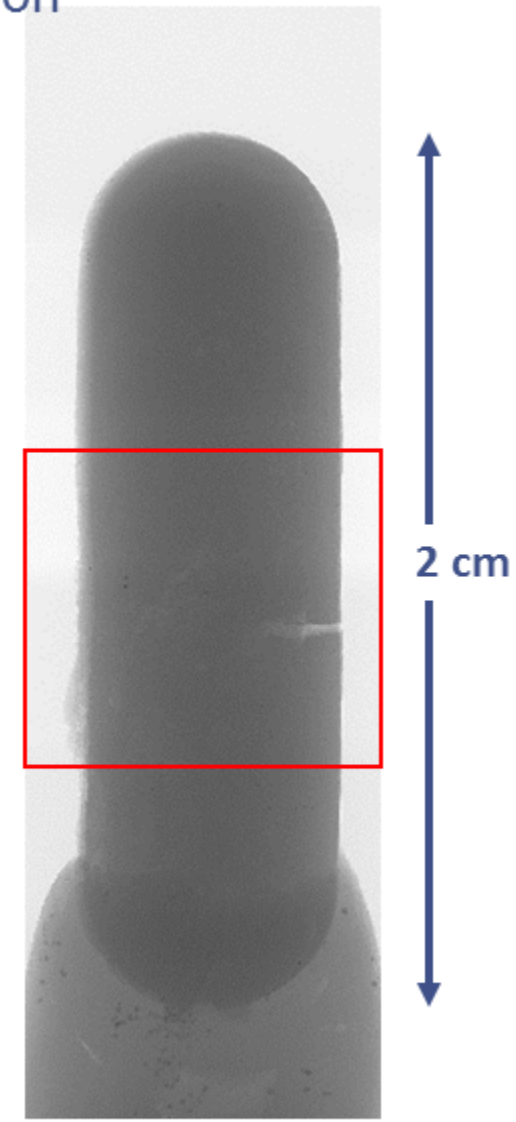
Analysis Settings:
Image Pixel Size 2.00 um (CCD-Detector)
Frame Average 4
Source Voltage (kV) = 40 / Current (uA) = 360

Tablet Size:
Minor Diameter 4.71 mm
Major Diameter 5.84 mm

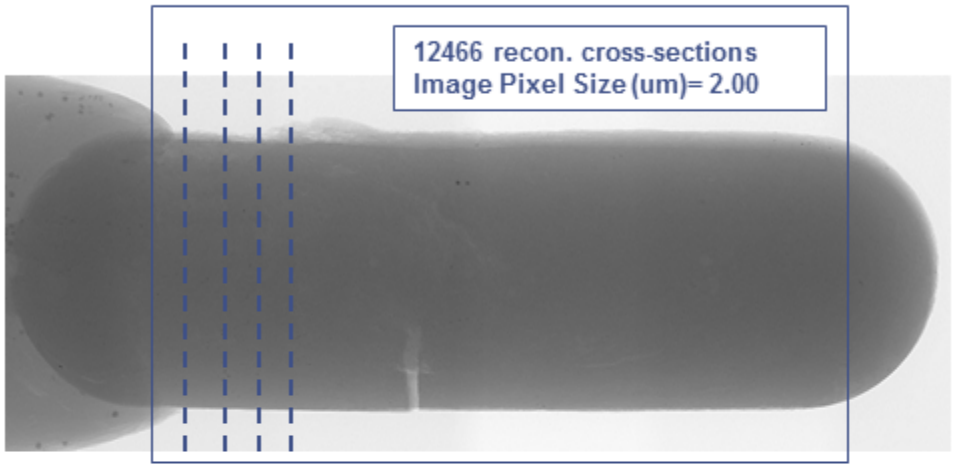
Tablet Porosity:
Closed 1.4 %
Open 1.7 %
Total 3.1 %

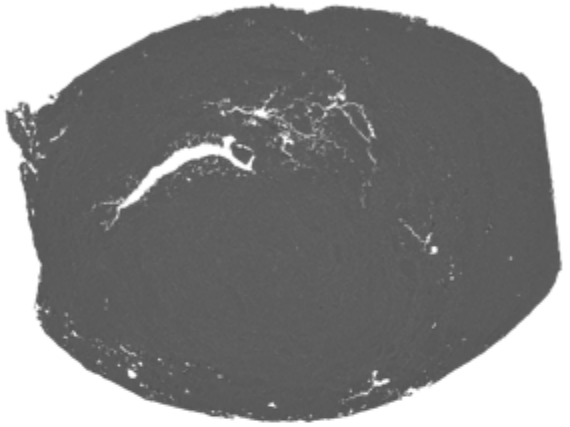




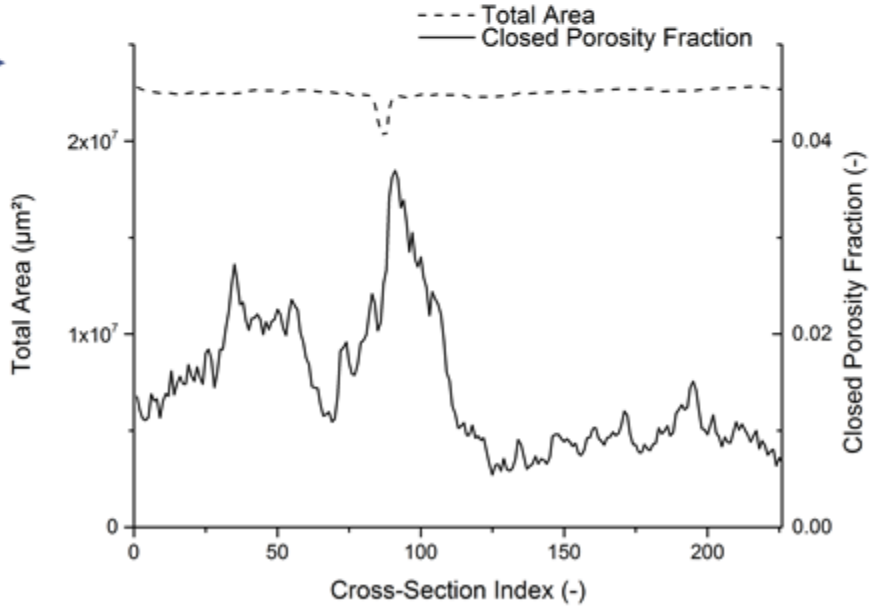


Injection Moulded Tablets:
Structural Characterisation





Cross-section Analysis:



3D Printed Tablets:
Introduction

- Commercial PVA filament loaded with drug by submerging in a methanolic solution containing desired drug for 24 hours.
- After drying in an oven, tablets were printed which varied in infill % between 10%, 50% and 90%.

3D Printed Formulated Systems: (Additive Manufacturing)

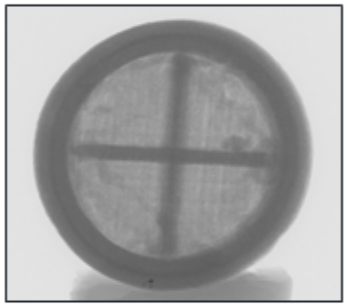
CAD Drawing

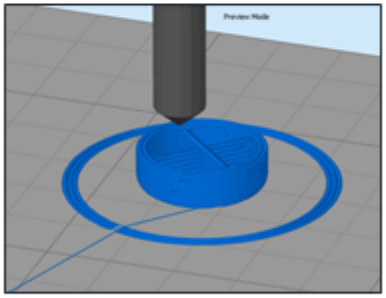
↓

Numerical Control Programming Language (G-Code)

↓

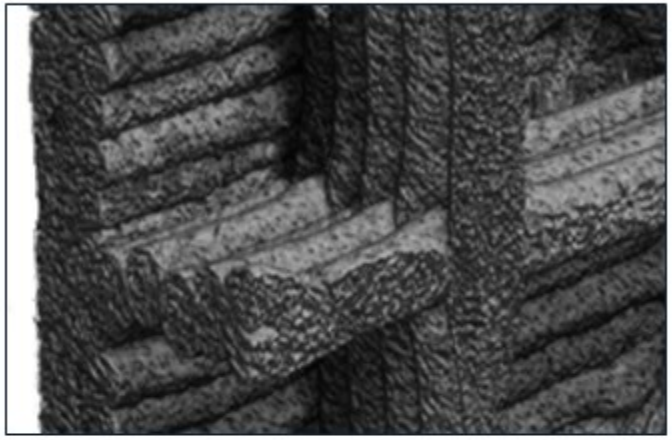
Manufacturing Process (3D Printer)





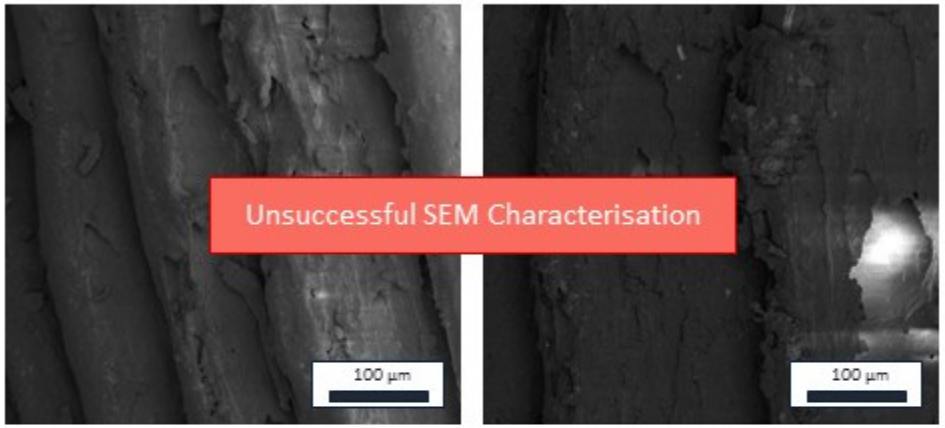
➡ **Use CT to evaluate printing process**

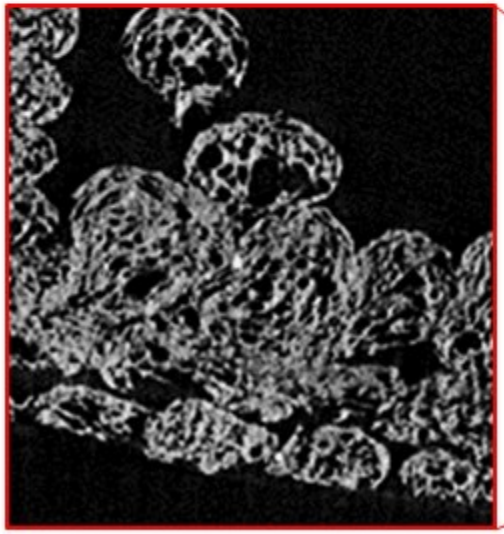
3D Printed Tablets:
Visualisation

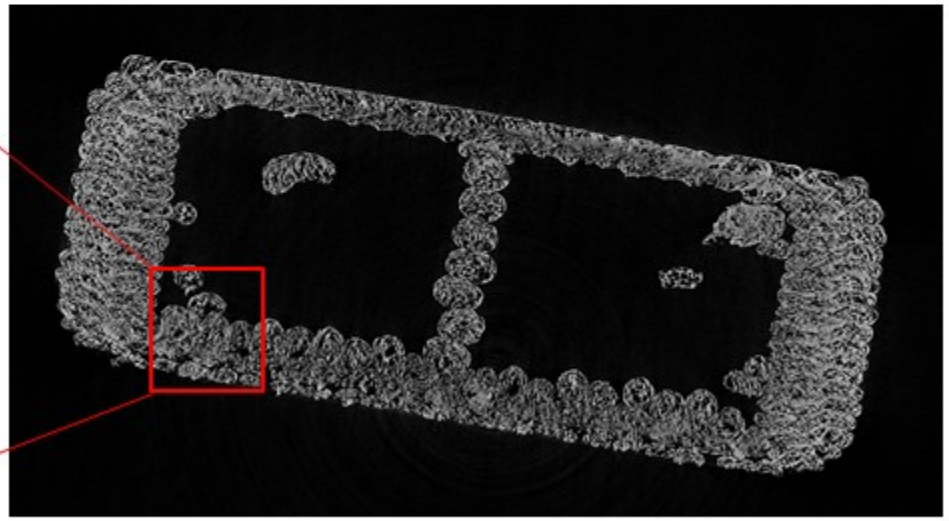


Pure PVA

PVA and Drug







3D Printed Tablets:
Structural Characterisation

Analysis Settings:

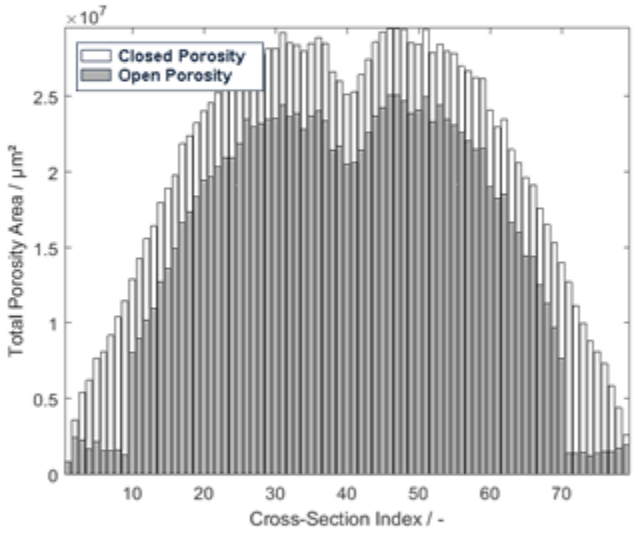
Image Pixel Size	4.2 um (CCD-Detector)
Frame Average	6
Source Voltage (kV)=	90 / Current (uA)= 180

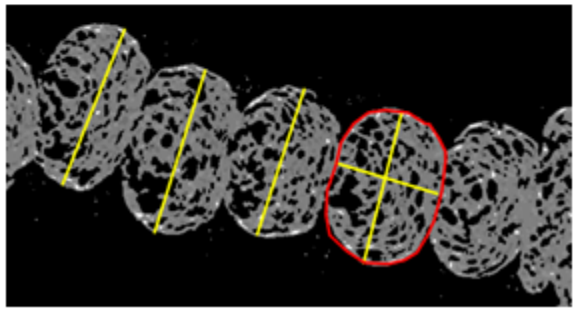
Tablet Size:

Radius	10.39 mm
Height	3.89 mm

Tablet Porosity:

Closed	16.3 %
Open	50.3 %
Total	66.6 %



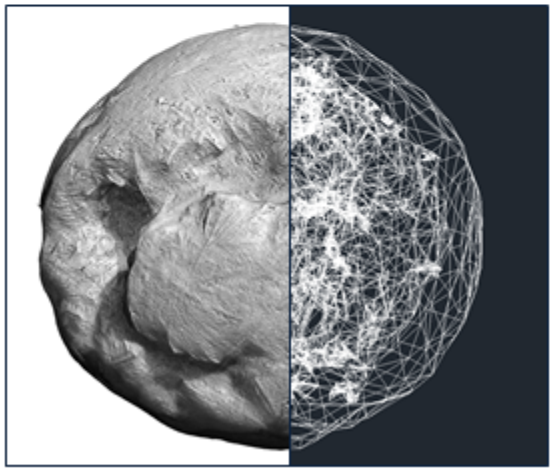


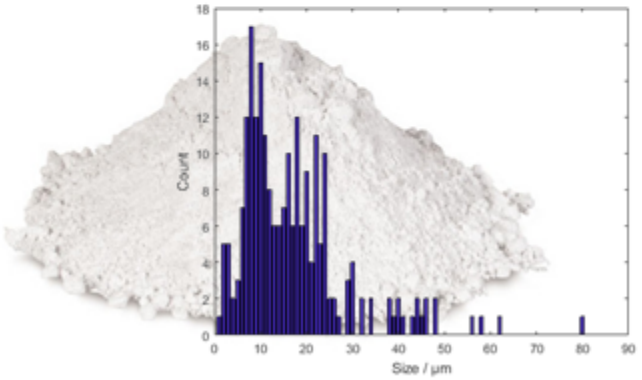
Filament Size Analysis (Manual):

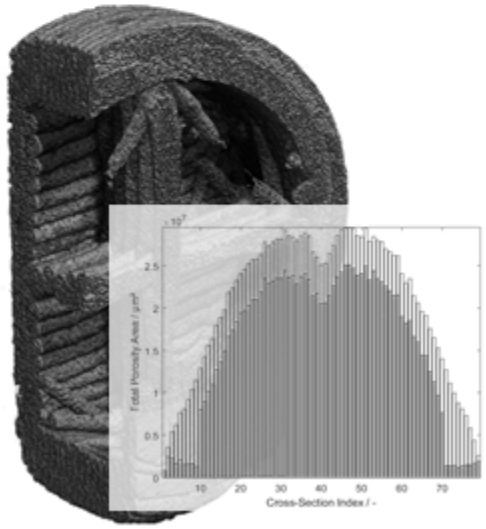
Mean Length	612.17 um +/- 30.41 um
Filament Width	387.24 um
Filament Area	3.97 10^5 um^2

Conclusion

- CT analysis can be used to non-destructively investigate the 3D structure of a vast variety of solid pharmaceutical products.
- Cross-Section Analysis can be applied to efficiently extract desired morphological descriptors of solid pharmaceutical products.
- The results can be directly employed to evaluate and improve production processes and enable a prediction of the (final) solid product performance.
- Future work will focus on a full 3D characterization of pharmaceutical samples and the investigation of phase uniformity on gray-scale.







Acknowledgements

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